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DOES THE DEGREE OF LUMINAL NARROWING OF SEGMENTS FREE OF RESTENOSIS 4 TO 12 MONTHS AFTER ANGIOPLASTY PREDICT LONG TERM OUTCOME?

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While cardiac events continue to occur in in patients (pts) free of angiographic restenosis after PTCA, it is not known whether late events are dependent on the remaining disease in previously dilated segments (D-site) or the extent of disease elsewhere in the coronary arteries (ND-site). The purpose of this study was to determine whether narrowing at D-site(s) and/or ND-site(s) present on angiographic follow-up in pts whose D-site had <50% diameter narrowing 4 to 12 months after PTCA correlates with late outcome. 1502 such pts were identified: 79% with 1 vessel disease, ejection fraction 59±12%. Revascularization was complete in 84% (99% for 1 vessel disease). Time to angiographic restudy documenting patency was 6.8±1.6 months. Clinical follow-up at 40±21 months was available in 1489 pts(99%). Pts were grouped according to % narrowing of ND-site(s) (none, <50%, >=50%) and of D-site(s) (<30%, 31%-49%) on angiographic restudy. Multivariate correlates of 6 year freedom from events (MI, PTCA, CABG, death): hypertension (p=0.006), diabetes (p=0.001), and % narrowing in ND-sites (p<0.0001).

	Freedom From Events	p value
% Narrowing ND-site(s)		
none	.74	<0.0001
<50%	.64	
≤50%	.52	
% Narrowing D-site(s)		
<30%	0.66	NS
31%-49%	0.65	

Conclusions: 1) In the absence of angiographically significant restenosis, the % narrowing is not an independent predictor of late outcome. 2) Late outcome in these pts is strongly dependent on the severity of disease elsewhere in non-dilated segments.

THE EFFECT OF DIABETES ON RESTENOSIS

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From a number of smaller studies diabetes (DM) appears to be an important risk factor for restenosis after PTCA. Few data are available with regard to type of DM and restenosis or the clinical presentation of restenosis in DM. To determine the relationship between DM and restenosis we evaluated 960 randomly selected patients (PTS) undergoing first time PTCA. Angiographic follow-up was obtained in 86% (n = 739) of PTS eligible by protocol at a median of 185 days. This population included 124 diabetics (17%) who were subdivided into insulin treated (INSULIN) (n = 33), oral hypoglycemic treated (ORAL) (n = 56) and diet treated (DIET) (n = 35) groups. Diabetics were less likely to have a history of hyperlipidemia or smoking and were more likely to be hypertensive. No differences in other baseline characteristics were noted. Restenosis rates (RR) are shown below:

Group	n	RR (%)	95% Conf Int (%)
non - DM	615	40	(36 - 43)
DM	124	55	(46 - 64)
INSULIN	33	58	(41 - 74)
ORAL	56	57	(44 - 70)
DIET	35	49	(32 - 65)
INSULIN or ORAL	89	57	(47 - 68)

It was also noted that there was no difference in the percentage of patients presenting with asymptomatic restenosis in DM vs non - DM (25% vs 29%).

These results reinforce that diabetes is a major risk factor for restenosis. The lack of an increased rate of asymptomatic restenosis in diabetes is surprising and further confuses the issue of silent ischemia in diabetes. The higher incidence of restenosis in pharmacologically treated (INSULIN or ORAL) diabetics (p = < 0.005) suggests potential roles for more severe diabetes or insulin in restenosis.

RESTENOSIS IN AN ATHEROSCLEROTIC RABBIT MODEL IS REDUCED BY A THIOL PROTEASE INHIBITOR.

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We have shown that the thiol protease inhibitor acetyl-leucyl-leucyl-norleucinal (TPI-1) reduces proliferation of smooth muscle cells in culture. Using a Wolinsky porous infusion catheter, we injected a solution of TPI-1 (50 μM) for 45s into atherosclerotic rabbit femoral arteries (art) (n=7) immediately following angioplasty to evaluate the effect of TPI-1 on restenosis. The contralateral artery (n=5) was injected with the carrier solution (control 1) and 12 atherosclerotic angioplastied but non-injected art were considered control 2. The animals were sacrificed after angiography at 2 weeks, the art were sectioned into 3mm segments and stained with hematoxylin/eosin and elastin/trichrome, and morphometry was performed. Results were evaluated by analysis of variance. Angiography showed a smaller decrease in minimal luminal diameter in the 2 weeks following angioplasty in the TPI-1 group (0.26±0.27mm vs 0.88±0.33mm for control 1 and 0.83± 0.36mm for control 2, p = 0.004). Histologic evaluation revealed a trend toward larger lumen area in the TPI-1 group (0.84±0.40mm^2 vs 0.55±0.19mm^2 for control 1 and 0.54±0.26mm^2 for control 2, p = 0.113). Neointimal area was unchanged between the groups (TPI-1 = 0.76±0.23mm^2, control 1=0.76±0.42mm^2, control 2=0.63±0.31mm^2; p = 0.817), but the neointima/media ratio was smaller in the treated art due to an increased medial thickness in these (0.76±0.38 vs 0.45±0.14 for control 1 and 0.38±0.05 for control 2, p = 0.02). These data demonstrate that intramural injection of a thiol protease inhibitor reduces post-angioplasty restenosis while preserving the medial layer. We hypothesize that the process of vascular remodeling after angioplasty is significantly modified by thiol protease inhibition.

ANGIOTENSIN CONVERTING ENZYME INHIBITION REDUCES RESTENOSIS IN EXPERIMENTAL ANGIOPLASTY.

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Angiotensin converting enzyme inhibition (ACEI) prevents myointimal proliferation after injury of the rat carotid artery. To determine whether this treatment also reduces restenosis (RS) after angioplasty (A) in a model of atherosclerosis, we gave cilazapril 5 mg/kg/day in food to 9 hypercholesterolemic rabbits with stenotic lesions in the iliac artery, starting 1 week (W) prior to iliac A and continuing until final angiography at 4 W. Treated animals had cilazapril levels of 62 ± 52 ng/ml, ACE activity of 1.79 ± 2.99 U/L and systolic blood pressure fell by 49.8 ± 23 mm Hg. Compared to nine controls (C) matched for similar pre and post-A lesion diameters, angiographic data showed:

	Luminal Diameter (mm, mean ± S.D.)			
	Pre A	Post A	4 W Post A	Difference
ACEI	0.82 ±0.22	1.24 ±0.30	0.96 ±0.20	-0.27 ±0.38
C	0.81 ±0.29	1.38 ±0.19	0.49 ±0.49	-0.89 ±0.51
p=	NS	NS	0.019	0.010

When RS is defined as loss of ≥ 50% of the initial post A gain, ACEI decreased the incidence of RS (2/9 ACEI vs 8/9 C, p=0.018). Histologically, the treated and untreated animals were qualitatively indistinguishable. These data indicate that ACEI begun prior to A significantly reduces the rate of RS in a hypercholesterolemic, atherosclerotic model of balloon A. The mechanisms underlying this effect are unknown. One might speculate that a reduction in angiotensin II may result in a decrease in the expression of proto-oncogenes and stimulation of smooth muscle cell protein production and hypertrophy.